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Animal models in research on retinal degenerations: past progress and future hope

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Abstract

The retinal degenerations (RDs) are a family of inherited retinal degenerative diseases (dystrophies) that lead to vision loss. Although phenotypically very different, the RDs have several characteristics in common. They all are caused by gene mutations or at least have a genetic component in the etiology. They all lead to photoreceptor dysfunction, many leading to the death of both rod and cone photoreceptors. The mechanism of cell death in most of the RDs seems to be through the process of apoptosis. It is estimated that more than fifteen million people around the world have vision loss due to an inherited RD. Many of these are patients with the dry form of age-related macular degeneration (AMD) who retain partial functional vision. However, some have other degenerative conditions such as retinitis pigmentosa, Leber congenital amaurosis or wet AMD and can suffer from severe vision loss or total blindness. © 2002 Published by Elsevier Science Ltd.

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1. Natural animal models

The good news for RD patients is that there are a number of natural animal models available for studying these diseases. Importantly, many of the genes found to be mutated in animals that result in a retinal degeneration (RD) have been found to be similarly abnormal in the human. Thus, in many ways, these animal models are true "models" in that they faithfully mimic the human disease genetically and also produce similar phenotypic conditions of vision loss. The importance of these models lies in several different areas. First, the animal models have given us a rich supply of candidate genes for testing in the human. Finding the animal gene mutation can be a long and arduous task but, once done, the gene can be quickly tested in the human, usually with rapid, positive results. Second, one can study the pathology and cell biology of the mutated gene and its gene product. Understanding, e.g., how a mutated protein of diminished or destroyed function subserves a particular cellular function could lead to development of a drug or natural substance to partially or even fully alleviate the block. Third, another important use, obviously, is in testing treatment regimens for efficacy and for safety. Demonstrating "proof of principle" in one or more animal models for presentation to the FDA can go far in moving a therapy towards human clinical trials. Similarly, demonstrating safety in one (preferably two or three) animal species allows for greater comfort in approaching human experiments and trials.

The natural animal models come in many forms, sizes, phyla and flavors—some even tasting like chicken. Low in phylogenetic classification but not in usefulness is the fruitfly (*Drosophila melanogaster*). This model has certainly been important in understanding normal pathways in the visual process. Moreover, with the large number of mutants available, the ability to breed up large numbers of animals and their short life cycle, the fruitfly has been a key animal model in pinpointing mutated genes that can lead to RD (Pak, 1995). At the vertebrate level, the zebrafish has many of the same characteristics, with large-scale screening able to be accomplished in a relatively quick and inexpensive manner (Brockerhoff et al., 1995). The chicken has the advantage of having a relatively large proportion of cone photoreceptor cells, somewhat similar to that of the human retina (Semple-Rowland & Lee, 2000).

RDs in mammals have long been recognized, the archetypes being the *rodless* mouse (Keeler, 1924), the RCS rat (Bourne, Campbell, & Tansley, 1938; Dowling & Sidman, 1962), and the retinal degeneration slow (*rds*) mouse models (Van Nie, Ivanyi, & Demant, 1978). The *rodless* mouse was the first mammalian RD described (1920s), and was later shown to be identical to the *rd*

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mouse, a now widely researched model of recessive RD (Pittler, Keeler, Sidman, & Baehr, 1993). The *rds* model was described in the late 70s and extensively characterized in the 80s by Prof. Somes Sanyal (Sanyal & Jansen, 1981). Larger animal models are also useful for all the reasons given above but are particularly important in establishing efficacy and safety parameters prior to human treatments. Several canine models of inherited RD have been identified, and in some cases, colonies of affected animals have been established. Aguirre and coworkers have identified and characterized several forms of canine RD with almost a dozen different models now available. These are mostly autosomal recessive conditions although an X-linked model is being characterized. The defect in the Irish Setter is particularly interesting since it exhibits the same defect in the cyclic GMP phosphodiesterase β-subunit gene observed in the *rd* mouse and in some human families with recessive retinitis pigmentosa (RP) (Aguirre, 1978; Suber et al., 1993). This gives the opportunity of studying faithful models of human RP disease both in small (mouse) and larger (dog) animals. Cat models of inherited RD have also been described. Autosomal recessive progressive retinal atrophy (PRA) in the Abyssinian cat has been particularly well characterized (Narfstrom, 1983). An autosomal dominant form of PRA has also been reported in this animal (Barnett & Curtis, 1985). Gene mutations in these feline models have yet to be elucidated.

2. Genetically engineered animal models

The not-so-good news for work on RDs is that the repertoire of natural models is limited. Most of the natural animal models are for recessive forms of RP, a good natural model for dominant RP, e.g., has yet to be found. Similarly, there is yet no exact model for dry age-related mascular degeneration (AMD) or for the choroidal vascularization found in wet AMD. The "exact" animal of choice for AMD, of course, would have to be a primate since only they have a macula as in the human. Finally, there are no exact models for many of the rare forms of RD, notably the forms of Usher syndrome. However, great progress has been made over the last few years in constructing bioengineered animal models that mimic the human diseases. Through transgenic animals, knockouts, etc., "new" models can be generated. To date, rodent and pig models have been engineered, notably, some expressing dominant forms of RD.

Many examples are now in the RD literature where transgenic mice have been produced bearing a mutated gene that leads to phenotypic RD. For example, Naash et al. introduced a mutated opsin gene into the mouse, producing a good simulation of the course of human autosomal dominant RP (Naash, Hollyfield, Al-Ubaidi, & Baehr, 1993). More recently, Hong et al. produced a murine model for X-linked retinitis pigmentosa (RP3) (Hong et al., 2000). Through gene knockout techniques, they created an *RPG*R-deficient model that resulted in both rod and cone cell degeneration. In these mutants, the pathobiology of the disease process can be elucidated. In this case, the *RPG*R mutation leads to a disruption of the unidirectional movement of opsin in the photoreceptor cell with resultant cell degeneration. Genetic engineering in a larger animal model has produced an excellent model for RP in the pig. The pig eye is not only similar in size to the human but has a fairly similar number and distribution of rod and cone cells. In a heroic undertaking, Petters et al. have produced a porcine model in which the degeneration is quite similar to human RP (Petters et al., 1997). The transgenic animals expressing a mutated opsin gene (*Pro*347Leu) have early rod loss with slower cone cell degeneration, making the pig a very attractive model for preclinical efficacy and safety trials.

Finally, progress is being made in developing models for general macular degeneration and AMD. For Stargardt disease and perhaps dry AMD, an *ABC*R (*ABC*A4) knock-out mouse was developed by Travis and coworkers (Weng et al., 1999) that simulates the human disease process in many aspects. For wet AMD, no model is yet fully representative of the macular and choroidal neovascularization seen in the human although some transgenic animals are available for studying intraretinal and subretinal new vessel growth in the mouse, e.g. (Okamoto et al., 1997).

3. Animal model uses: candidate genes and pathobiology

Rapid screening of visual mutants in *Drosophila* and examination of genes important to normal *Drosophila* visual function has been useful in pinpointing genes causing RD in the human. Mutations in the human homolog of the *Drosophila crumbs* gene, e.g., has been found to cause pigment epithelial cell abnormalities and RD in patients of the RP12 phenotype (den Hollander et al., 1999). Important work on the *rd* chicken has lead to the identification of a null mutation in the photoreceptor-specific guanylate cyclase gene that causes a RD analogous to the human condition of Leber's congenital amaurosis (LCA) (Semple-Rowland, Lee, Van Hooser, Palczewski, & Baehr, 1998).

As with the chicken, much work over many years has finally led to elucidation of the gene (*MER*TK) causing the phagocytosis problem and ensuing RD in the RCS rat (D'Cruz et al., 2000). Rapidly thereafter, mutations in the human ortholog to this gene were found to cause RP (Gal et al., 2000). In the *rds* mouse, Travis and coworkers cloned the gene in the late 80s and soon identified the gene product as a structural protein restricted

to and stabilizing photoreceptor outer segment discs (Travis, Brennan, Danielson, Kozak, & Sutcliffe, 1989; Travis, Sutcliffe, & Bok, 1991). Because of its importance in photoreceptor cell biology in maintaining outer segment integrity, mutations in peripherin/rds are now known to be involved in over 40 types of human RDs, e.g. (Keen & Inglehearn, 1996). These range from types of RP to progressive macular degenerations (Wells et al., 1993). This is a prime example of the "ripple effect" where genetic analysis of a single animal model can lead to wide ranging advances in understanding several forms of human RD disease.

An excellent example of the usefulness of animal models in the convergence of normal cell biology and pathobiology studies on the photoreceptor neuron is seen in work on the *ABC*A4 gene. It is now clear that the well known rim protein (RmP) is identical to the more recently characterized *ABC*A4 gene product whose mutation(s) cause Stargardt disease (Azarian & Travis, 1997). In the *ABC*A4 knockout mouse (Weng et al., 1999), both electrophysiological and morphological signs of RD are produced. In particular, deposition of the lipofuscin fluorophore A2E is seen in the RPE layer, possibly resulting in "poisoning" of the RPE cells and secondary loss of photoreceptor cells. Recent work with the *abc*r−/− mutant clearly demonstrates inhibition of A2E formation in mice raised in darkness, implicating light as a factor in at least some RDs (Mata, Weng, & Travis, 2000). Evidence from cell biological studies indicates that the *ABC*A4 protein is a fairly specific target for photooxidative damage in the photoreceptor neuron and that individuals with "diminished *ABC*R activity" may be at particular risk to photodamage (Sun & Nathans, 2001).

Finally, animal work has been generally helpful in clarifying the question of light damage to photoreceptors and in producing a "light-damage model" for simulation of RD which can be used to test possible therapies. Light damage and ensuing photoreceptor cell death have been known for several decades now (Noell, Walker, Kang, & Berman, 1966). The biological mechanism of such damage, however, is only recently being unraveled. It is now known that the apoptotic cell death induced by light damage is dependant on the presence of functional rhodopsin in the photoreceptor. Studies on tansgenic mice expressing mutant forms of rhodopsin suggested a link between light damage and the presence of active rhodopsin (Naash et al., 1996). More recently, Grimm et al. have used *RPE*65-deficient mice to demonstrate the central role of rhodopsin in generation or transduction of the "death signal" and that the transcriptional factor AP-1 is a key element in light-induced cell death (Grimm et al., 2000). Induction of the specific heat shock protein HO-1 had previously given strong evidence that light "insult" resulted in oxidative damage to the retina (Kutty et al., 1995) as had been postulated by Organisciak and coworkers (Organisciak, Darrow, Jiang, Marak, & Blanks, 1992).

4. Animal model uses: preclinical testing

Having an adequate animal model(s) is of almost overriding importance in preclinical testing of any potential treatment. Small inexpensive animal models can be very useful in the earlier phases of investigation where larger numbers of subjects are generally needed. Larger-sized animal models can then be used to fine tune the results and better address the questions of safety, dose, delivery, etc. Certainly, the FDA wants to see adequate evidence for efficacy and for safety prior to approval of human clinical trials. Also, establishing these parameters is often helpful in persuading a biotech or pharmaceutical company to move to the human trials. So far, scientific "proof of principle" has been established in a number of animal models for at least partial efficacy in the areas of transplantation, pharmaceutical therapy and gene therapy.

One of the early positive uses of animal models in exploring therapies for RD was in the transplantation study by Turner and coworkers (Li & Turner, 1988). In this study and many thereafter from several laboratories, the efficacy and relative safety of RPE cell transplants was demonstrated in the RCS rat model. Proof of efficacy for photoreceptor transplantation has been more elusive although light-driven ganglion cell responses have been reported in *rd* mice after transplantation of young (13 day) host retina (Radner et al., 2001). More recently, transplantation studies have been expanded to examine the possible use of stem (progenitor) cells in photoreceptor replacement. Young and coworkers, e.g., have demonstrated a level of neuronal differentiation and morphological integration of hippocampal progenitor cells transplanted into the retina of the RCS rat (Young, Ray, Whiteley, Klassen, & Gage, 2000). Interestingly, a positive effect on cone survival in the RD mouse was reported recently employing selective transplantation of rod photoreceptor cells, opening up questions of rod–cone interaction and survival factor production, among others (Mohand-Said, Hicks, Dreyfus, & Sahel, 2000). An excellent review of the transplant field and the use of animal models has been recently published (Lund et al., 2001).

Another important use of animal models is in the area of pharmaceutical therapy—i.e., the study of drugs, growth factors and natural substances that function as neuron-survival agents to slow down or even halt the progression of the retinal degenerative disease process. The seminal work of LaVail, Steinberg and coworkers first demonstrated the efficacy of one of the neuron-survival agents, bFGF, in slowing the progression of the RD of the RCS rat (Faktorovich, Steinberg, Yasumura,

Matthes, & LaVail, 1990). Since then, numerous animal models have been used to demonstrate the neuronal protective effect of several different agents on the dystrophic retina (LaVail et al., 1998). This "proof of principle" along with the relative safety of most of the agents tested in the animal models indicates the feasibility of human clinical trials at some point in the future.

Other potentially neuroprotective agents have been tested in animal models, some with positive results. The use of orally administered retinoids has been found to result in "dramatic improvement in rod physiology" in *RPE*65-deficient mice, ostensibly allowing for bypass of the block in the visual cycle caused by the mutation (Van Hooser et al., 2000). Somewhat similarly, vitamin A supplementation "significantly reduced the decline of *a*-wave and *b*-wave amplitudes" in the *T17*M opsin mutant mouse but did not do so in the *P347*S mutant (Li et al., 1998). This is an important finding since it could lead the way in defining human genetic subsets that are or are not amenable to a particular treatment. In the light-damage rodent model, 13-*cis* retinoic acid (RA) was found to protect photoreceptors from light-induced degeneration (Sieving et al., 2001). Since administration of 13-*cis* RA markedly slowed rhodopsin regeneration among other effects, it was suggested that "strategies of altering retinoid cycling may have therapeutic implications for some forms of retinal and macular degeneration". Also in the light-damage model, a variety of antioxidative agents have been shown to be protective (Organisciak et al., 1991; Kutty et al., 1995). Halothane (Keller, Grimm, Wenzel, Hafezi, & Reme, 2001) and glucorticoid activation (Wenzel et al., 2001) appear to both be neuroprotective in the rhodopsin-mediated, light-damage model. These very positive results point out another need in moving towards RD therapies—i.e., effective means of drug delivery to the retina. This area of investigation is just beginning but, as the potential therapies multiply, animal model experiments should lead the way in determining the best method of getting effective doses of protective agents to the posterior segment of the eye.

The canine models can also be used effectively for studies on efficacy and safety of treatment regimens—not always with positive results. Miniature poodles with progressive rod–cone degeneration (*prcd*) exhibit decreased levels of docosahexaenoic acid (DHA, 22:6n-3) much as seen in some human patients with RP and Usher syndrome. If this biochemical deficit results from a primary genetic problem, it was reasoned (Aguirre, Acland, Maude, & Anderson, 1997) that DHA replacement therapy through the diet might slow or even reverse the cause of the disease. Although DHA supplementation was not found to alter the course of the *prcd* phenotype, it did demonstrate the usefulness of the model in efficacy testing. Similar negative results have been obtained when the use of a calcium channel blocker was not found to slow the RD in the *rcd1* canine model of RD carrying a null mutation in the *PDE*6B gene (Pearce-Kelling et al., 2001). These results are different from those in the *rd* mouse (with an identical gene defect) where D-*cis*-diltiazem did provide partial protection to photoreceptors and visual function (Frasson et al., 1999). Perhaps species specificities account for these differences? In the dog, much more success has been recently demonstrated in gene therapy efficacy trials in the Briard dog as described in the next section.

Proof of principle for gene therapy has now been well established in both rodent and canine RD models. Bennet and coworkers were the first to definitively demonstrate photoreceptor rescue by gene replacement therapy in the *rd* mouse (Bennett et al., 1996). Subretinal injection of Ad-CMV-βPDE elicited increased PDE enzyme activity in the retina and delayed photoreceptor death by several weeks. Recent work by Ali et al. not only demonstrated partial restoration of outer segment integrity in *rds* mice with a peripherin mutation but functional restoration of an ERG signal as well (Ali et al., 2000). Besides autosomal recessive disease models, autosomal dominant models can be bioengineered and used for efficacy trials using ribozyme gene therapy. Lewin and coworkers have done just that and successfully showed photoreceptor rescue in a transgenic rat model of ADRP carrying a rhodopsin (*P23*H) mutation (Lewin et al., 1998). In the same rat model, the efficacy of such treatment was recently shown even if applied after significant photoreceptor loss (LaVail et al., 2000). Moreover, the long-term (>8 months) efficacy of the treatment was demonstrated. Thus, both recessive and dominant forms of RP can be addressed by simple gene replacement therapy or knock-down strategies, respectively, with satisfactory efficacy and safety. It is important to note, however, that Dudus et al. have reported significant levels of the reporter protein, green fluorescent protein (GFP), in the optic nerves and brains of mice and dogs following intravitreal injection of rAAV-GFP (Dudus et al., 1999). This finding certainly necessitates follow-up work prior to human clinical trials.

Techniques of pharmaceutical therapy and gene therapy can be effectively combined to deliver a number of neuroprotective agents to the retina (CNTF, BDNF, etc.) as well as genes and their products that are known to be neuroprotective (e.g., *bcl*-2). Abitbol and coworkers, e.g., have shown delayed photoreceptor cell degeneration after injection of a bFGF2 construct into the eye of the 3 week old RCS rat (Neuner-Jehle et al., 2000). Similarly, *bcl*-2 overexpression in transgenic mouse models of RP (opsin and PDE mutants) as well as in a light-damage model resulted in decreased photoreceptor degeneration (Chen et al., 1996). A protective effect of *bcl*-2 gene therapy was also seen in the *rds* mouse model (Nir, Kedzierski, Chen, & Travis, 2000).

Finally, recent gene therapy work in a larger animal model is perhaps the best example of the possibility of

not only sight preservation but sight restoration (Acland et al., 2001). The Briard dog exhibits a congenital, severe loss in vision similar to human children with LCA. Affected animals within this breed are *RPE*65−/−, leading to the vision defect. Using an AAV-*RPE*65, very successful restoration of visual function was demonstrated not only with fairly robust ERG responses but positive psychophysical responses to simple visual cues. Importantly, the effect seems to be persistent and gives great hope for successful human gene therapy, at least for this particular inherited RD.

5. Conclusion

The search for natural animal models of RD has been long but exceedingly successful. Modern techniques of molecular biology have added significantly to the models available for study. However, significant gaps yet are present in our animal armamentarium. For example, better models for AMD, dry and wet, are needed. Recent activity in primate bioengineering, though, may give us these models. The cell biology and pathophysiology of the AMD degenerative process can then be better studied and manipulated. Ultimately, though, the most important aspect of animal model research will be in their usefulness for demonstration of efficacy and safety of the many treatment regimens under study for all the inherited degenerations. This exciting prospect now seems to be a close reality in all the areas described above. If we can "treat" or "cure" these diseases in animals, why not the human?

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